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STRESS RESPONSE IN CHRONIC HYPERCAPNIA

by

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SUMMARY PAGE

THE PROBLEM

To determine the time course of the stress response during prolonged continuous exposure and intermittent exposure to carbon dioxide.

FINDINGS

Respiratory acidosis induced in guinea pigs exposed to 15 per cent carbon dioxide in 21 per cent oxygen for seven days was compensated after three days. Adrenal cortical response, as measured by a rise of blood corticosteroids, adrenal cholesterol depletion, and lymphopenia, was limited to the three-day phase of uncompensated respiratory acidosis. Intermittent daily eight-hour exposure to 15 per cent carbon dioxide for seven days did not produce a compensation of the respiratory acidosis, nor an abatement of the stress response.

APPLICATIONS

Findings provide important information on the mechanisms involved in the stress response to chronic and intermittent exposure to carbon dioxide, which still represent significant problems in submarine medicine.

ADMINISTRATION INFORMATION

This investigation was conducted as a part of Bureau of Medicine and Surgery Work Unit MF022.03.03-9028 - Time-Concentration Exposure Limits of Carbon Dioxide. The manuscript of this report was approved for publication on 4 August 1967 (Clearance No. 666). It was sent to the American Journal of Physiology and subsequently published in that journal, Vol. 214, No. 3, March 1968. This reprint has been designated as Submarine Medical Research Laboratory Report No. 524. It is Report No. 1 on the Work Unit shown above.

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Stress response in chronic hypercapnia

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SCHAEFER, KARL E., NANCY McCABE, AND JUDITH WITHERS. *Stress response in chronic hypercapnia.* Am. J. Physiol. 214(3): 543–548. 1968.—Respiratory acidosis induced by prolonged exposure of guinea pigs to 15% CO_2 in 21% O_2 was compensated after 3 days of exposure. Adrenal cortical response as measured by a rise of blood corticosteroids, adrenal cholesterol depletion, and lymphopenia was limited to the 3-day phase of uncompensated respiratory acidosis. The same was true for adrenal medullary stimulation as indicated by adrenal epinephrine depletion. Free fatty acid levels did not change during the 1st hr of exposure to 15% CO_2, but showed a 100% rise after 6 hr of exposure and returned to initial levels with the compensation of the respiratory acidosis. Intermittent daily 8-hr exposure to 15% CO_2 for 7 days did neither produce a compensation of the respiratory acidosis nor an abatement of the sympathoadrenal stimulation. Significant changes in body weight consisting in a 10% loss occurred only during the first 2 days of exposure to 15% CO_2. Adrenal enlargement and lymphatic involution accompanying the sympathicoadrenal response to respiratory acidosis outlasted the functional changes and were still present after 7 days of exposure to 15% CO_2.

adrenal cortical and adrenal medullary response; uncompensated and compensated respiratory acidosis; stress of CO_2; free fatty acids in chronic hypercapnia; blood corticosteroids; epinephrine

STRESS OF CO_2 has been investigated mostly under conditions of acute exposure to elevated CO_2 concentrations, which was shown to produce an adrenal cortical as well as adrenal medullary stimulation. Fortier (4) found a typical stress reaction with adrenal hyperplasia in rats which had been kept for 3 days in an atmosphere containing 15% CO_2, 19% O_2, and 66% N_2.

Langley and Kilgore (7) presented evidence of adrenal cortical stimulation as measured by adrenal cholesterol and ascorbic acid depletion in rats after 4-hr exposure to CO_2 concentrations ranging from 10 to 30% CO_2. Richards and Stein (15) found an increase in 17-hydroxycorticosteroids in adrenal venous blood in anesthetized dogs exposed to 2.5, 5, 10, 20, and 30% CO_2 for 1 hr. Adrenal cortical stimulation was minimal at 2.5% CO_2 with 1 out of 10 dogs responding with an acute rise of adrenal steroids and maximal at 20% CO_2. Under the latter condition the whole group of eight exposed animals reacted with a maximum increase in adrenal steroid output. Further experiments on the influence of altered acid-base balance on adrenal cortical function in anesthetized dogs were reported by Richards (14). He demonstrated that changes in both factors, arterial pH as well as CO_2 tension, can independently act as a pituitary adrenal cortical stimulus. Inhalation of CO_2 concentrations between 10 and 15% CO_2 were found to cause a release of catecholamines as measured with a bioassay technique (21). Using a chemical method for the determination of catecholamines increased blood catecholamine levels were observed following acute exposure to 25% CO_2 (8).

The few studies done on the stress effect in chronic hypercapnia were limited to low concentrations of 1.5 and 3% CO_2 which seem to indicate existence of a continued adrenal response. Exposure of rats and guinea pigs to 1.5% CO_2 for 42 days resulted in a decrease of adrenal cholesterol and ascorbic acid levels, lymphopenia, and eosinopenia (5). Exposure to 3% CO_2 for periods up to 17 days produced a decrease in epinephrine content of the adrenal glands associated with morphological changes (19).

The question as to whether the sympathoadrenal response to CO_2 is a specific CO_2 effect or caused by hydrogen ion changes has not been answered unequivocally. Evidence favoring a specific CO_2 effect has been obtained in experiments in which the CO_2-produced increases in blood catecholamine levels were not significantly altered by simultaneous administration of bicarbonate preventing a fall in pH (21). However, in studies of apneic oxygenation, which results in a strong sympathoadrenal response (8), infusion of an organic buffer (THAM) abolished the rise of plasma epinephrine (9). In chronic hypercapnia induced by exposure to 15% CO_2, the phases of uncompensated and compensated respiratory acidosis are clearly delineated and compensation is usually accomplished within 3 days (16). This paper presents evidence that under these conditions the sympathoadrenal response is limited to the uncompensated phase of respiratory acidosis and, therefore, clearly pH dependent.

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METHODS

Male guinea pigs of the Hartley strain weighing between 400 and 600 g were exposed to 15% CO_2 in air (21% O_2). The gas mixtures were prepared in the laboratory by mixing pure CO_2 with compressed air and O_2 in high-pressure cylinders. These were analyzed with the Scholander apparatus. A plastic chamber was employed for the experiments. The animals were carefully selected. After arrival at the laboratory, the guinea pigs were housed in individual cages and measurements of body weight were made for 3–4 days. Only animals that gained weight and had a leukocyte count below 11,000 were used in the experiments. The carbon dioxide concentration in the chamber was continuously monitored with a Beckman infrared CO_2 analyzer and the oxygen content intermittently with a Beckman O_2 analyzer. The CO_2 concentrations were kept at 15% within limits of ±0.5% and the oxygen concentration at 21% ± 1%. The exposure chamber was installed in an air-conditioned room. A closed-circuit system within the chamber circulated air continuously through silica gel containers. With these means the environmental temperature was kept at 78 ± 2 F. and the humidity at 65–75%. Ammonia vapor was absorbed by boric acid placed in a second closed circuit within the chamber. The exposure chamber was opened every morning for a period of about 3–5 min to fill the water and food containers and to take out the urine and feces.

Prior to sacrifice, the animals received 40 mg pentobarbital per kilogram weight subcutaneously and were returned to the CO_2 exposure chamber within 4–5 sec. The anesthesia was usually effective after approximately 5 min, at which time the animals were taken out of the exposure chamber and immediately placed under a mask through which they breathed the same CO_2 gas mixture to which they had been exposed. Blood samples were drawn from the abdominal aorta. Blood pH was determined with an Instrumentation Laboratory blood gas and pH analyzing system. Blood corticosteroids were determined with the technique of Silber, Busch, and Oslapas (20).

Epinephrine content of the adrenals was measured using the method of Anton and Sayre (1). The adrenal tissues were immediately frozen until used. Nonesterified free fatty acids were determined with the technique of Dole (3) as modified by Trout et al. (23). Adrenal cholesterol was measured according to the method of Kingsley and Schaffert (6). Organ weights were obtained in a separate series of experiments as part of histopathological studies. The organs were excised and weighed to 0.10 mg using a Christian-Becker balance.

RESULTS

Exposure of guinea pigs to 15% CO_2 in 21% O_2 for 7 days resulted in a precipitous loss of body weight amounting to about 10% during the first 2 days followed by a rapid gain during the subsequent exposure period (Fig. 1). Initial values were reached between 5 and 7 days. During the recovery period on air, animals increased their body weight at a rate corresponding to that measured during the control period. The effect of chronic hypercapnia on organ weights of adrenals, thymus, para-arterial nodes, and spleen expressed in percent body weight is shown in Fig. 2.

Adrenal weights were found significantly increased after 1 day and remained elevated for 7 days. Thymus, para-arterial nodes and spleen showed a marked fall in weight during the 1st day and did not return to initial values during the 7-day exposure period with the exception of the spleen, which showed a short transitory decrease limited to 1 day. After an extended exposure for 20–40 days to 15% CO_2, most of the organ weights

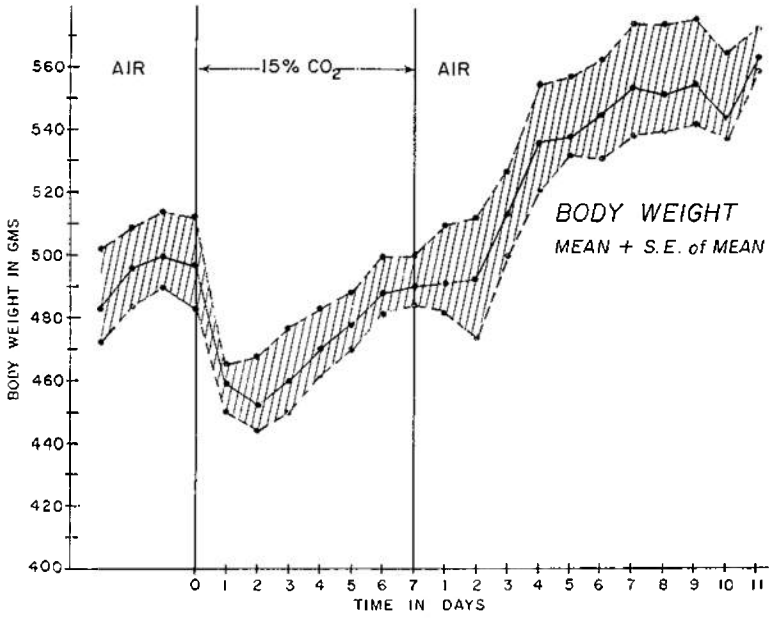

FIG. 1. Effect of 7 days exposure of guinea pigs to 15% CO_2 in 21% O_2 and subsequent recovery on air for 11 days on body weight. Twelve guinea pigs. Means and SE of the mean.

(expressed in percent body weight) had returned to approximately normal values with the exception of the thymus weight, which remained lower. Similar observations were made after a recovery period of 11 days following a 7-day exposure to 15% CO_2. In this case most of the organ weights had reached initial values. However the adrenal weight increase still persisted.

The behavior of acid base balance (pH of arterial blood) adrenal cortical (blood corticosteroids), adrenal medullary response (adrenal epinephrine content), and epinephrine-dependent effects (free fatty acids) during chronic hypercapnia are displayed in Fig. 3.

The pH fell to the lowest point (7.00) after 1 hr of exposure to 15% CO_2, rose to 7.10 after 6 hr and remained at this level during the 1st day, but increased 0.1 pH units on each of the subsequent 2 days. After 3 days the respiratory acidosis induced by inhalation of 15% CO_2 was practically compensated.

Both blood corticosteroid increase and adrenal epinephrine depletion were limited to the 3 days of uncompensated respiratory acidosis. The same is true for the rise in free fatty acids. Extended exposure to 15% CO_2 for 15 days did not produce significant changes in the values measured after 7 days of exposure.

Adrenal cholesterol values, total leukocytes and total

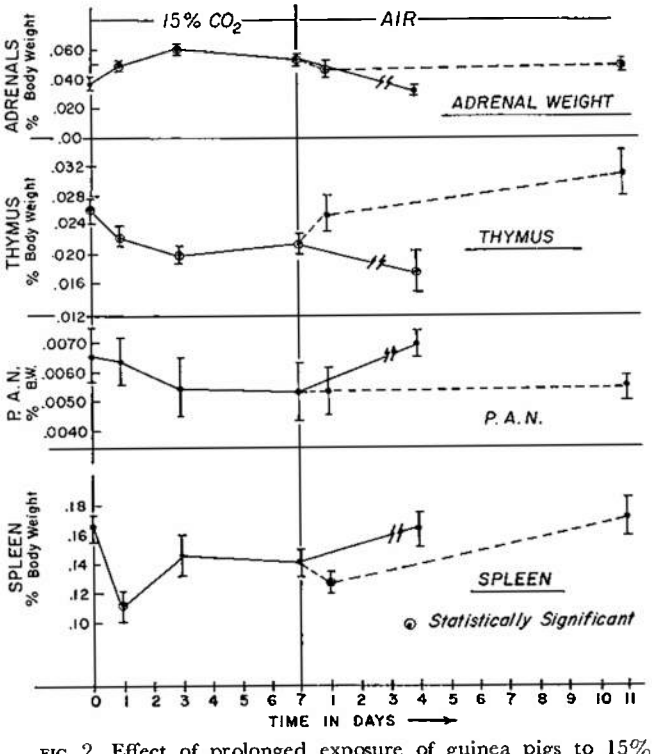

FIG. 2. Effect of prolonged exposure of guinea pigs to 15% CO_2 in 21% O_2 on organ weights (adrenals, thymus, para-arterial nodes, spleen). Organ weights expressed in percent body weights. Dotted line connects data obtained at 1 and 11 days of recovery on air following 7 days of exposure to 15% CO_2. Interrupted solid line (⟩⟨) data of animals continuously exposed from 20–40 days. Means and SD of means. ⊙ Data statistically significantly different from control values at the 5% level and better. Control groups 30 animals, experimental group 15–28.

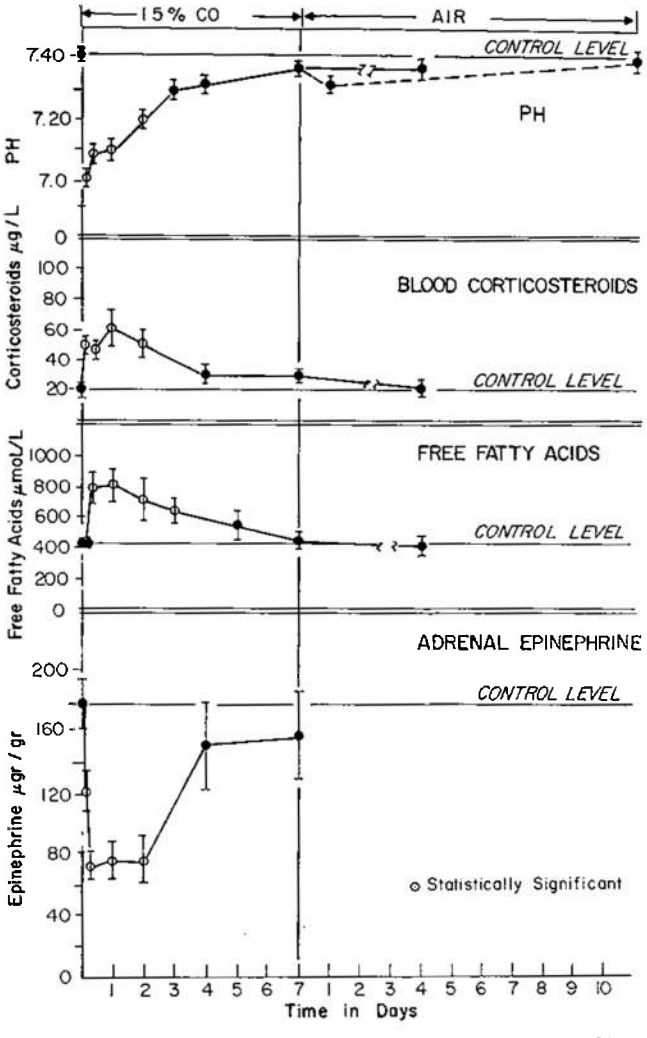

FIG. 3. Effect of prolonged exposure to 15% CO_2 in 21% O_2 on pH, corticosteroids, free fatty acids of arterial blood, and epinephrine content of the adrenal glands in guinea pigs. Means and SE of the means. ⊙ Data statistically significantly different from control values at the 5% level and better. Control group 15 animals, experimental group 8–15.

lymphocytes of guinea pigs exposed to 15% CO_2 for various periods of time are listed in Table 1 and 2. A significant decrease in adrenal cholesterol as well as a marked lymphopenia indicative of adrenal cortical stimulation was found to be limited to the 3-day period of uncompensated respiratory acidosis. The transition to air following a 7-day period of exposure to 15% CO_2 also resulted in a transitory adrenal cortical stimulation as seen in the decrease of adrenal cholesterol and lymphopenia during 1-day recovery.

Data for pH, blood corticosteroids, and adrenal epinephrine content of guinea pigs exposed intermittently 8 hr daily for 7 days to 15% CO_2 in 21% O_2 are compared in Table 3 with control data and values obtained after 7 days of continuous exposure to 15% CO_2. It is quite evident that animals exposed intermittently to 15% CO_2 for 7 days do neither attain a compensation of the

respiratory acidosis nor the associated decline of the sympathoadrenal response.

DISCUSSION

Before evaluating the results of these experiments it is necessary to assess the influence of the anesthetic on the acid-base status of the animals. Pontén and Siesjö (11) recently measured the arterial CO_2 tension in rats prior to injection of barbiturate and after attainment of surgical anesthesia and found an average increase of 4.7 mm Hg. It was noted that the amount of anesthetic used had little influence on the arterial CO_2 tensions. In two different series of experiments a decrease of 2–3 mEq/liter in bicarbonate concentration and corresponding reduction in pH was found in anesthetized rats as compared with data obtained in unanesthetized animals. The effects of surgical anesthesia in small animals on extracellular pH are rather small (0.07 pH units) and it is questionable whether during the short period of anesthesia intracellular pH changes could occur. The large alteration in pH produced by exposure to 15% CO_2 in guinea pigs (0.40 pH units) would not be influenced significantly by the effects of anesthesia. Since the latter are superimposed in both control and experimental animals, all the measured blood pH values are a little too low, but the time course of the uncompensated and compensated respiratory acidosis is not altered by the anesthesia effects.

TABLE 1. *Effect of prolonged exposure to 15% CO_2 in 21% O_2 on adrenal cholesterol content of guinea pigs*

Condition	Adrenal Cholesterol, mg/100 g	
	Mean ± SD	N
Control	6.1±.80	10
Exposure to 15% CO_2 in 21% O_2		
1 hr	4.52*±.96	8
1 day	4.02*±1.1	20
2 days	3.85*±1.3	6
3 days	5.86±1.9	12
4 days	5.90±1.6	6
5 days	6.30±1.3	8
6 days	7.34±2.15	6
7 days	6.92±1.54	7
15 days	5.15±1.45	8
42 days	7.64±1.28	5
Recovery on air following 7 days of exposure to 15% CO_2		
1 day	4.73†±1.2	17
11 days	5.28±.82	13

* Differences from controls statistically significant at the 1% level ($P < .01$). † Differences statistically significant when compared with data obtained at 7 days of exposure to 15% CO_2 ($P < .01$).

The present study demonstrates that the CO_2-induced adrenal cortical and adrenal medullary response represents an unspecific pH-dependent effect. Compensation of the respiratory acidosis was found to be associated with an abatement of the sympathoadrenal response. Further evidence for the pH dependence of the latter is shown in the results of experiments with intermittent exposure to 15% CO_2 for 7 days, which failed to produce a compensation of the respiratory acidosis and resulted in a persistence of the sympathoadrenal response. Based on measurements of tissue CO_2 content in lungs of guinea pigs exposed to 15% CO_2, intracellular pH was calculated and found to follow with a few hours lag time the CO_2-induced fall in extracellular pH and returned after 3 days of exposure to near normal levels commensurate with the recovery of extracellular pH (18). Thus the two phases of uncom-

TABLE 2. *Effect of prolonged exposure to 15% CO_2 in 21% O_2 on white blood cell counts and number of total lymphocytes of guinea pigs*

Conditions	White Blood Cells, cells/mm³		Total Lymphocytes, cells/mm³		
	Mean ± SD	N	Mean ± SD	N	*P*
Exposure to 15% CO_2 in 21% O_2					
Control	5,840±2,033	15	3,820±1,047	15	
1 day	6,715±2,669	15	2,240*±1,500	15	.01
Control	5,667±2,225	15	3,490 ±597	15	
2–3 days	4,647±1,513	15	2,296*±634	15	.001
Control	5,400±1,713	20	3,188±1,097	15	
4–7 days	6,257±1,221	20	3461±1,165	15	
Control	5,800±1,296	7	4,019±1,137	5	
15 days	5,471±1,247	7	4,055±1,109	5	
Control	7,900±1,380	5	5,495±1,175	5	
42 days	7,270±1,128	5	4,825±825	5	
Recovery on air following 7 days of exposure to 15% CO_2					
Control	5,707±1,716	14	4,871±1,027	14	
1-day recovery	4,185±1,215	14	2,742*±796	14	.05
Control	5,100±1,100	7	3,815±1,071	7	
11-days recovery	5,300±1,350	7	3,151±881	7	

* Differences from controls statistically significant at the 5% level and better. Each experimental group served as its own control.

TABLE 3. *Stress effect of intermittent 8-hr exposure to 15% CO_2 in 21% O_2 for 7 days as compared with that of continuous 7-day exposure*

Conditions		pH	Blood Corticosteroids, mg/liter	Adrenal Epinephrine, μg/g
Control	Mean ± SD	7.410±.025	29.0±12.8	179.3±42.0
	N	15	11	10
15% CO_2				
7 days continuous exposure	Mean ± SD	7.37±.035	32.3±13.9	150.9±73.0
	N	8	8	8
7 days intermittent exposure sacrificed end of 8 hr CO_2 exposure	Mean ± SD	7.111*±.07	72.1*±31.5	107.4*±38.3
	N	5	5	(5)
7 days intermittent exposure sacrificed end of 16 hr on air	Mean ± SD	7.396±.130	67.6*±35.4	106.4*±20.1
	N	5	(5)	5

* Differences from controls statistically significant at the 5% level and better (t test).

pensated and compensated respiratory acidosis, displayed in the time course of blood pH changes, corresponded in general with intracellular pH changes. These findings support the assumption that the stress response in chronic hypercapnia is dependent on extracellular and correlated intracellular pH changes.

In our previous studies involving prolonged exposure of guinea pigs and rats to 3% CO_2 and 1.5% CO_2, existence of a continuous adrenal response was suggested (5, 19). However, sampling periods were too infrequent in these studies to establish a precise relationship with the acid-base balance equilibrium. Moreover, the time periods required to reach a compensation of the respiratory acidosis are much longer during exposure to low concentrations of CO_2. In more detailed studies of human subjects exposed for 42 days to 1.5% CO_2 the uncompensated phase of respiratory acidosis was found to last 24 days (17). Further studies of prolonged exposure of guinea pigs and rats to low concentrations of CO_2 are required to determine the extent of the sympathoadrenal response and whether there is a pH dependence under these conditions.

The results of the present investigation also demonstrate a close interaction of adrenal cortical and adrenal medullary responses. After 1 hr of exposure to 15% CO_2 blood corticosteroids have significantly increased and the adrenal epinephrine content has markedly declined indicating a release of catecholamines. However, the free fatty acid level did not change during this period in spite of the endogenous epinephrine release. A further increase of the epinephrine release after 6-hr exposure to 15% CO_2 results in a rise of free fatty acid levels to twice normal. Both free fatty acid values and adrenal epinephrine content return to initial values with the compensation of the respiratory acidosis which demonstrates the pH dependence of the sympathoadrenal stimulation in chronic hypercapnia. The action of endogenous epinephrine on free fatty acid relase is not inhibited by hypercapnic acidosis in contrast to the inhibition of the lipolytic effect of epinephrine infusions in anesthetized dogs, ventilated for 1 hr with a gas mixture of 10% CO_2 in 25% O_2 (12). Under these conditions the external epinephrine stimulus is applied to a system already responding to CO_2 with an epinephrine release which modifies the response. This notion is supported by findings, indicating that both liberation of endogenous epinephrine and inhibition of the lipolytic action of exogenous epinephrine are pH dependent (10).

The stress of exposure to 15% CO_2 produces a drastic drop in body weight during the first 2 days, which according to our observations must be related to a marked decrease in food intake during this period. Organ changes associated with the stress response, adrenal enlargement, and involvement of lympathic organs are clearly expressed after 1 day of exposure. The thymus gland weight appears to be continuously depressed during CO_2 exposure, whereas the weight of adrenal glands and that of the periarterial nodes return to control values after 20 days of exposure but not during the 4 days of compensated respiratory acidosis within the 7-day exposure period. This demonstrates a time lag between functional changes expressed in blood corticosteroids and adrenal epinephrine responses and total organ weight changes.

It should be noted also that the spleen, which is known to function as a blood store (2) and to contract in response to CO_2 inhalation and adrenaline infusion (13), shows a significant weight decrease after 1 day of exposure to 15% CO_2 during the uncompensated phase of respiratory acidosis and returns to approximately normal values after 3 days of exposure associated with the compensation of the respiratory acidosis which suggests a pH dependent spleen contraction. Transition from CO_2 to air has been shown to produce a further adrenal response in experiments with short exposure to CO_2 (21, 22). Although the recovery response following chronic hypercapnia has not been investigated in regard to such sensitive parameters as blood corticosteriod levels and adrenal epinephrine content, lymphopenia and a significant decrease found in adrenal cholesterol after 1-day recovery on air following 7 days of exposure to 15% CO_2 seem to give support to the notion, that withdrawal of CO_2 following chronic hypercapnia causes a stimulatory effect on the adrenals. The cause of this CO_2 withdrawal response has still to be determined.

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13. ABSTRACT

Respiratory acidosis induced by prolonged exposure of guinea pigs to 15% CO_2 in 21% O_2 was compensated after 3 days of exposure. Adrenal cortical response as measured by a rise of blood corticosteroids, adrenal cholesterol depletion, and lymphopenia was limited to the 3-day phase of uncompensated respiratory acidosis. The same was true for adrenal medullary stimulation as indicated by adrenal epinephrine depletion. Free fatty acid levels did not change during the 1st hr of exposure to 15% CO_2, but showed a 100% rise after 6 hrs of exposure and returned to initial levels with the compensation of the respiratory acidosis. Intermittent daily 8-hr exposure to 15% CO_2 for 7 days did neither produce a compensation of the respiratory acidosis nor an abatement of the sympathoadrenal stimulation. Significant changes in body weight consisting in a 10% loss occurred only during the first 2 days of exposure to 15% CO_2. Adrenal enlargement and lymphatic involution accompanying the sympathicoadrenal response to respiratory acidosis outlasted the functional changes and were still present after 7 days of exposure to 15% CO_2.

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